Turkish Psychological Articles, June 2022, *25*(49), 21-26 DOI: 10.31828/tpy1301996120211203m000043

Summary

The Effects of Long-Term Cocoa Flavanols Intake on Cognitive Functions and Mood, and the Physiological Mechanisms Underlying These Effects: A Literature Review

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Flavanols are a subclass of flavonoids, a group of natural compounds found in plant-based foods. They are abundant in nutrients, including cocoa, grapes, apples, black and green teas (Gu et al., 2004). Cocoa has a special place as it contains the greatest amount of flavanols among other flavanol-containing nutrients (Lee et al., 2003). Over the last two decades, researchers from various disciplines investigated the health benefits of cocoa-derived products containing flavanols. For instance, cocoa flavanols (CF) intake was proven to reduce platelet aggregation, blood pressure, and insulin resistance (Corti et al., 2009). In this paper, studies examining the effects of long-term CF intake on cognitive functions and mood and the physiological mechanism underlying these effects are reviewed.

Physiological Effects of Cocoa Flavanols

CF contains monomeric flavanols –in the form of epicatechin and catechin– and oligomeric/polymeric flavanols known as procyanidin (Lazarus et al., 1999). Absorption of CF in the form of epicatechin readily occurs in the human digestive system, and its concentration reaches the greatest level in blood plasma 2-3 hours after ingestion (Nehlig, 2013). In an animal study, epicatechin and catechin molecules have crossed the blood-brain barrier (van Praag et al., 2007), accumulating in specific brain regions that are more vulnerable to the adverse effects of aging, such as the hippocampus, cerebellum, and striatum (Socci et al., 2017). Similarly, CF has been suggested to prevent cognitive decline via its neuroprotective properties (Nehlig, 2013). Moreover, there is empirical evidence that flavonoids have pharmacological activity on enzymes, receptors, and signaling pathways (Hanrahan et al., 2011). For example, CF intake enhances the expression of brain-derived neurotrophic factor (BDNF) in memory-related brain structures and the blood serum (Neshatdoust et al., 2016; Socci et al., 2017). BDNF deficiency in the hippocampus and substantia nigra is associated with Alzheimer's and Parkinson's diseases, respectively (Bathina & Das, 2015; Binder & Scharfman, 2004). Besides, low BDNF level is associated with depression and anxiety (Sleaiman et al., 2016). Collective evidence suggests that CF consumption may improve cognitive functions and mood by increasing the BDNF level.

Together with its direct effects, CF has indirect effects on the brain and cognitive functions. An epidemiological study demonstrated that cardiovascular diseases are less common in Kuna Indians who consume cocoa products corresponding to an average of 900 mg CF per day (Corti et al., 2009). Cardiovascular risk factors play a role in the pathophysiology of disorders accompanied by various cognitive impairments, such as Alzheimer's disease and mild cognitive impairment (Grassi et al., 2016). Cerebral blood flow in which the neurons are supplemented with oxygen and glucose must be at a certain level for a normal functioning brain. Since CF ingestion causes flow-mediated dilation (Fisher et al., 2003) and increases cerebral blood flow (Francis et al., 2006), CF is thought to facilitate cognitive functions indirectly.

The Role of Nitric Oxide in the Physiological Effects of Cocoa Flavanols

Physiological effects of flavanols are associated with the synthesis of nitric oxide (NO) within blood vessels (Karim et al., 2000; Fisher et al., 2003; Heiss et al., 2003). Although NO has numerous biological functions, its vasodilatory effect and role as a retrograde neurotransmitter could explain the relationship between CF intake and improved cognitive functions (Karabay et al., 2018). Two recent studies showed that CF intake improves cognitive performance by reducing insulin resistance (Desideri et al., 2012; Mastroiacovo et al., 2014) which may be mediated by NO synthesis.

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Effects of Long-Term Intake of Cocoa Flavanols on Cognitive Functions

In the so-called Cocoa, Cognition, and Aging (CoCoA) studies, the effects of daily CF intake for eight weeks on cognitive functions were assessed both in older adults with mild cognitive impairment (Desideri et al., 2012) and cognitively intact senior subjects (Mastroiacovo et al., 2014). In both studies, high and low-dose CF intake compared to placebo enhanced working memory, mental flexibility, and processing speed measured by Trail Making Test A&B. Similar results were observed in the Verbal Fluency Task requiring verbal ability, selective attention, and response inhibition. Besides, insulin resistance and blood pressure decreased among subjects exposed to low and high CF administration. The improvement in cognitive functions was predominantly associated with reduced insulin resistance. Hence, these studies demonstrated that long-term CF intake supports cognitive functions by improving insulin sensitivity.

Brickman et al. (2014) investigated the chronic effect of CF consumption on memory performance and cerebral blood volume (CBV) in the dentate gyrus using fMRI. After three months of dietary intervention, older adults in the flavanol condition improved their performance in the ModBent test measuring pattern separation ability. The faster reaction time of 630 ms was found to correspond to an improvement in memory performance equivalent to about three decades of aging. Additionally, CF intake increased CBV in the dentate gyrus which was positively correlated with performance in ModBent. Although the physiological mechanism underlying this alteration in memory functions is not fully explored, the formation of new blood vessels (angiogenesis), the production of new neurons (neurogenesis), and the formation of synapses (synaptogenesis) in the dentate gyrus following CF consumption might have led to the observed outcomes.

Neshatdoust et al. (2016) examined the relationship between serum BDNF level and cognitive functions following 12 weeks of CF intervention. Participants consumed flavanol-rich and flavanol-poor (control) cocoa beverages with a 4-week washout between supplementation periods. The neuropsychological test battery administered includes tasks in which a wide range of cognitive functions are assessed, including executive function, attention, episodic memory, and processing speed. Serum BDNF level and global cognition score significantly increased only after CF intervention. The positive correlation between BDNF and cognition showed that CF intake enhances cognitive functions by improving BDNF level.

Contrary to the aforementioned studies, there is evidence that CF intake has no impact on cognition. Francis et al. (2006) used fMRI to measure blood oxygenation level-dependent (BOLD) signal in response to task-switching test requiring switching between two sets of rules. Although BOLD signals increased in the anterior cingulate cortex, prefrontal cortex, and parietal cortex following five days of CF intake, no improvement was observed in the behavioral measures. It should be noted that there was no room for improvement in the task performance which may explain the lack of behavioral effects.

In another study, participants consuming a dark chocolate bar with a cup of cocoa beverage containing either 41 or 755 mg flavanols for six weeks completed a series of neuropsychological tests (Crews et al., 2008). Interestingly, they found no evidence that CF intake improves cognitive functions and cardiovascular health despite the high dose CF used. One possible reason for the null results is that cocoa products used in this experiment contain a meager amount of epicatechin (Haskell-Ramsay et al., 2018).

Massee et al. (2015) investigated the subchronic effect of CF on cognition by isolating flavanols from other cocoa components. Cognitive performance was evaluated using Swinburne University Computerized Cognitive Assessment Battery and Cognitive Demand Battery after participants took either active (250 mg CF) or placebo tablets (0 mg CF) daily for four weeks. However, the consumption of active tablets did not make a difference in overall cognitive functioning. The lack of effects was attributed to the low flavanols dose.

In terms of dose and duration, a similar study was implemented by Pase et al. (2013). In their study, middle-aged participants who consumed a cocoa beverage containing 0, 250, or 500 mg of CF for 30 days were subjected to Cognitive Drug Research Computerized Assessment System measuring attention and memory functions. Nevertheless, no difference in cognitive performance was observed between CF conditions.

Finally, Sorond et al. (2013) applied neuroimaging techniques to examine the link between cognitive functions and neurovascular coupling (NVC), and the effects of CF consumption. Older adults with vascular risk factors consumed either 1218 or 26 mg CF daily for a month. Afterward, they completed Mini-Mental State Examination and Trail Making Test A&B. The results demonstrated that participants with intact NVC showed a better cognitive performance. Regardless of CF dose, cocoa consumption improved NVC and Trail Making Test B performance in participants with impaired NVC. Although there was no control group for a fair comparison, observing the same effects in both conditions suggests that other components of cocoa may have an impact on NVC and executive functions.

Effects of Long-Term Intake of Cocoa Flavanols on Mood

Cocoa products, especially chocolate, are generally associated with pleasure and happiness. Carbohydrates, phenylethylamine, caffeine, tryptophan, anandamide, and magnesium are the main cocoa components thought to play a role in regulating mood. The effects of these bioactive components have been reviewed elsewhere (see: Nehlig, 2013; Tuenter et al., 2018). There are only a few randomized controlled trials addressing whether long-term CF consumption exerts any effect on mood. Nevertheless, there is strong evidence that the physiological changes caused by CF could regulate mood (Smith, 2013; Tuenter et al., 2018). For example, low BDNF level (Sleiman et al., 2016), increased oxidative stress (Westfall & Pasinetti, 2019), and reduced global cortical blood flow (Sackeim et al., 1990) are some of the important factors involved in the pathophysiology of depression. Based on the findings that CF intake increases antioxidant activity (Lee et al., 2003), BDNF level (Neshatdoust et al., 2016), and cerebral blood flow (Francis et al., 2006), the effects of CF consumption on anxiety, depression, fatigue, and stress have been examined (Table 1).

Sathyapalan et al. (2010) studied the effect of CF intake on symptoms of chronic fatigue syndrome by using several self-report questionnaires. After eight weeks of supplementation, the symptoms of chronic fatigue syndrome were significantly reduced in subjects consuming flavanol-rich chocolate reflected with improved scores in depression, anxiety, mental and physical fatigue questionnaires. Similar findings were obtained in the London Handicap Scale, in which general quality of life was evaluated. However, due to the limited sample size and the use of only self-report questionnaires, the findings of the study should be considered carefully.

Massee et al. (2015) used cocoa tablets to assess the effect of CF intake on mood and mental fatigue assessed by the Visual Analogue Scale. However, no effects on these variables were found in young participants when compared to placebo tablets. The insufficient dose of CF used in this study might account for the lack of effects on mood and fatigue.

In contrast, CF intake has been shown to positively affect mood in a study in which a higher dose was administered (Pase et al., 2013). Participants receiving a cocoa beverage containing 0, 250, or 500 mg CF for 30 days completed Bond-Lader Visual Analogue Scale at baseline and after treatment. Compared to the low dose and placebo, the high dose of CF intake improved self-rated calmness and contentedness. The positive effects of CF on mood and anxiety are partially related to polyphenols' regulatory function that binds to the benzodiazepine binding site of the $GABA_A$ receptors (Hanrahan et al., 2011; Medina et al., 1997). Benzodiazepines are drugs that have anxiolytic properties and benzodiazepines are used to treat anxiety disorders (Carlson, 2013). Thus, CF may support mood by acting as an agonist on GABA receptors.

Ibero-Baraibar et al. (2016) explored the effect of CF intake on mood, anxiety, and dopaminergic activity in overweight or obese subjects on an energy-restricted diet. Half of the subjects were on a low-calorie diet for four weeks, while the others followed the same diet with cocoa supplementation. The plasma homovanillic acid (HVA), positively correlated with dopaminergic activity responsible for mood, increased in both groups. Compared to the control group, the HVA concentration was greater in the experimental group. However, no significant differences in depression and anxiety were observed between groups. Instead, the symptoms of depression measured by the Beck Depression Inventory were reduced in all subjects. The researchers noted that alleviation of depressive symptoms might be a result of weight loss following an energy-restricted diet.

More recently, Fox et al. (2019) investigated the effect of chocolate consumption on anxiety and depression by using combined positron emission tomography-computed tomography (PET-CT). Healthy subjects consuming both flavanol-absent white chocolate and flavanol-rich dark chocolate completed the Hospital Anxiety and Depression Scale (HADS). No differences were observed in the HADS scores following five days of consuming dark chocolate, and these results were supported by the images obtained from the PET-CT scan. Compared to white chocolate, dark chocolate consumption had no impact on the activity of brain structures responsible for emotions, such as the amygdala. However, it should be taken into account that the different amounts of methylxanthines (caffeine and theobromine) in dark and white chocolate might have masked the effects of CF.

Conclusions

In recent years, randomized controlled trials have been conducted examining the effects of CF on cognitive functions and mood (see Table 1)**.** Studies addressing the physiological effects of CF intake on NO synthesis, vasodilation, blood flow, and insulin sensitivity have been sufficiently replicated, and consistent results have been obtained. However, the findings in studies examining cognitive functions and mood differ considerably, contrary to physiological effects. Research design (parallel vs. crossover), the CF content (e.g., epicatechin), CF dose, and administration duration are some essential factors accounting for contradictory outcomes.

Table 1. Summary of Studies Examining the Effects of Long-Term Cocoa Flavanols Intake on Cognitive Functions and/or Mood

Reference	Sample	Design	Duration (days)	CF Dose	Main Findings
Francis et al. (2006)	16 subjects (16 females; 18-30 years)	Randomized, Double-Blind, Placebo-Controlled, Crossover	5	172 mg (flavanol) *and* 13 mg (control)	BOLD signals increased in response to the task switching test in the flavanol condition. No differences were observed between flavanol and control conditions in the task-switching test.
Crews et al. (2008)	90 subjects (52 females; mean age:69)	Randomized, Double-Blind, Placebo-Controlled, Parallel	42	755 mg (flavanol) *or* 41 mg (control)	There are no significant differences in cardiovascular parameters (e.g. systolic/diastolic blood pressure) and cognitive functions between flavanol and control conditions.
Sathyapalan et al. (2010)	10 subjects with CFS (mean age:59)	Randomized, Double-Blind, Placebo-Controlled, Crossover	56	950 mg (flavanol) *and* 10 mg (control)	In the flavanol condition, fatigue (measured by CFQ), depression and anxiety symptoms (measured by HADS), and quality of life (measured by LHS) have improved.
Desideri et al. (2012)	90 subjects with MCI (64-82 years)	Randomized, Double-Blind, Placebo-Controlled, Parallel	56	990 mg (high), 520 mg (low) *or* 45 mg (control)	In the high and low dose CF condition, blood pressure and insulin resistance decreased, performance in the Trail Making Test A and B increased. In all conditions, especially in the high and low doses, performance in the Verbal Fluency Test improved.
Camfield et al. (2012)	63 subjects (40-65 years)	Randomized, Double-Blind, Placebo Controlled, Parallel	30	500 mg (high), 250 mg (low) *or* 0 mg (control)	No significant differences in the spatial working memory task were observed between the groups. SSVEP responses differed in posterior parietal and centro-frontal regions between all conditions.
Pase et al. (2013)	72 subjects (40-65 years)	Randomized, Double-Blind, Placebo-Controlled, Parallel	30	500 mg (high), 250 mg (low) *or* 0 mg (control)	No difference was found between groups in the CDR measuring cognitive functions. Calmness and contentedness scores improved following 30 days of high CF consumption.
Sorond et al. (2013)	60 subjects with VRF (mean age:73)	Randomized, Double-Blind, Placebo-Controlled, Parallel	30	1218 mg (flavanol) *or* 26 mg (control)	In both conditions, NVC and performance in Trail Making Test B improved in subjects with impaired NVC at baseline.

Brickman et al. (2014)	37 subjects (50-69 years)	Randomized, Double-Blind, Placebo-Controlled, Parallel	90	900 mg (flavanol) *or* 10 mg (control)	The cerebral blood volume in the dentate gyrus and the reaction time in the ModBent Test improved (630 ms faster) in the flavanol condition.
Mastroiacovo et al. (2014)	90 subjects (65-85 years)	Randomized, Double-Blind, Placebo-Controlled, Parallel	56	993 mg (high), 520 mg (low) *or* 48 mg (control)	In the high and low dose CF condition, blood pressure and insulin resistance decreased, performance in the Trail Making Test A and B increased. In all conditions, especially in the high dose, performance in the Verbal Fluency Test improved.
Massee et al. (2015)	40 subjects (18-40 years)	Randomized, Double-Blind, Placebo-Controlled, Parallel	28	250 mg (flavanol) *or* 0 mg (control)	No difference in cognitive performance (measured by SUCCAB and CDB) and cardiovascular measures (cerebral blood flow and blood pressure) were observed between the flavanol and control groups.
Neshatdoust et al. (2016)	40 subjects (18 females; 65-72 years)	Randomized, Double-Blind, Placebo-Controlled, Crossover	28	494 mg (flavanol) *and* 23 mg (control)	Serum BDNF level and general cognitive performance increased in the flavanol condition.
Ibero-Baraibar et al. (2016)	47 subjects with obesity (mean age:57)	Randomized, Double-Blind, Placebo-Controlled, Parallel	28	645 mg (flavanol) *or* control	No difference was found between two groups in terms of anxiety (measured by STAI) and depression (measured by BDI) symptoms. The plasma HVA level of subjects in the flavanol condition increased.
Fox et al. (2019)	16 subjects (21-58 years; mean age:34)	Randomized, Single-Blind, Placebo-Controlled, Crossover	5	250 mg (flavanol) *and* 0 mg (control)	No difference in anxiety and depression symptoms (measured by HADS) was observed between flavanol and control conditions. In the high CF condition, glucose metabolism increased within the occipital, motor, somatosensory, and prefrontal cortices.

BDI, Beck Depression Inventory; BOLD, Blood-Oxygen Level-Dependent; BDNF, Brain-Derived Neurotrophic Factor; CDB, Cognitive Demand Battery; CDR, Cognitive Drug Research computerized assessment system; CF, Cocoa Flavanols; CFS, Chronic Fatigue Syndrome; CFQ, Chalder Fatigue Scale; HADS, Hospital Anxiety and Depression Scale; HVA, Homovanillic Acid; LHS, London Handicap Scale; ModBent, Modified Benton Visual Retention Test; MCI, Mild Cognitive Impairment; NVC, Neurovascular coupling; PET-CT, Positron Emission Tomography-Computed Tomography; SSVEP, Steady-State Visually Evoked Potential; STAI, State-Trait Anxiety Inventory; SUCCAB, Swinburne University Computerized Cognitive Assessment Battery; VRF, Vascular Risk Factor

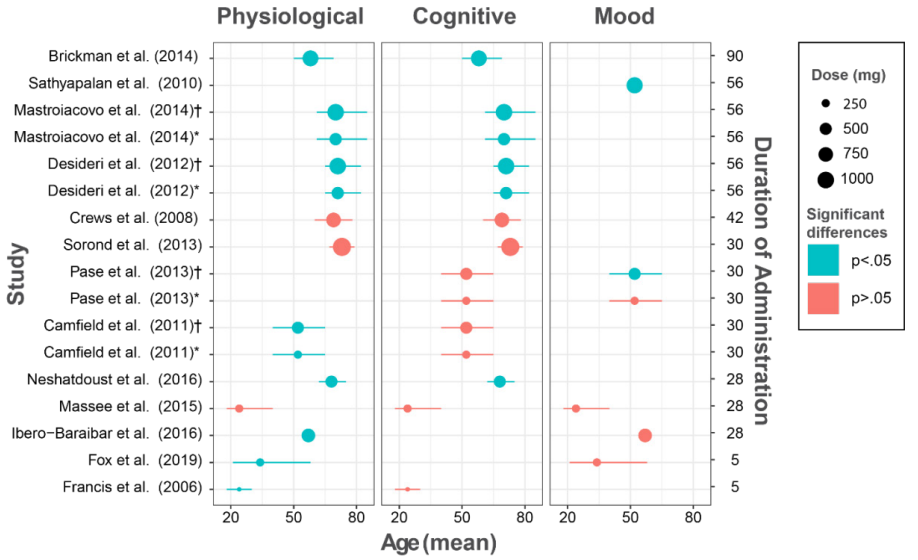

Figure 1. The effects of long-term cocoa flavanols intake on physiology, cognition, and mood as a function of age, dose, and administration duration.

The X-axis shows the age; Y-axis shows the list of studies and the administration duration (days). The horizontal lines indicate the age range, the location of the points indicates the mean age of the participants in the study, and the size of the points indicates the dose. The blue color indicates studies in which the effects of long-term CF intake were statistically significant (p <.05) in at least one of the measurements. The red color indicates that long-term CF intake did not affect any variable tested. Figure 1 was made based on the comparison between the flavanol condition and the control/placebo condition (not shown in the figure) in each study. Studies in which two different doses of CF were administered were depicted as independent studies. In the studies in which two different doses of CF were administered, † represents high-dose CF, whereas * represents low-dose CF.

To our knowledge, there is no study directly examining the effects of CF intake on physiology, cognition, and mood in terms of the dose and duration. However, it can be concluded that CF intake induces physiological responses even in low doses and in a shorter duration of administration. The contribution of the physiological response to cognitive functions and mood usually occurred with a longer CF intake. There is a pattern showing that longer CF intake predicts positive effects on these variables, regardless of dose. The pattern in Figure 1 shows that CF intake supports cognitive functions and mood in studies where the administration duration is at least eight weeks.

In vivo and *in vitro* studies conducted with humans and experimental animals show that long-term CF intake improves cognitive functions and mood by increasing the bioavailability of nitric oxide, which has a variety of functions, including dilating blood vessels, acting as a neurotransmitter, and improving insulin sensitivity. Furthermore, strong evidence has been presented that CF, which has high antioxidant activity and neuroprotective properties, could support cognitive functions in cognitively intact individuals and prevent cognitive decline that inevitably occurs with aging through direct actions on receptors, enzymes, and signaling pathways. Despite the mixed findings observed in CF studies, long-term intake of CF, depending on the dose and administration duration, regulate mood and support various cognitive functions.